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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/705,791	11/10/2003	Kenneth Chien	041673-1202	5197

7590 06/19/2007

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EXAMINER	
SGAGIAS, MAGDALENE K	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
06/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/705,791	CHIEN ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,19 and 24-31* is/are pending in the application.

4a) Of the above claim(s) *25-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-19 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/23/07 has been entered.

Applicant's arguments filed 4/23/07 have been fully considered but they are not persuasive. Claims 18-19, and 24-31 are pending. Claims 25-31 are withdrawn. Claims 1-17, 20-23, and 32-35 are canceled. Claims 18-19 and 24 are under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-19 and 24 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are directed to a method for treating a loss of cardiac muscle contractility associated with heart failure comprising: delivering an expression vector encoding a phospholaban (PLB) molecule having a single point mutation consisting of S16E or a double point mutation consisting of K3ER14E to myocytes, wherein the expressed molecule

accelerates SERCA2 mediated calcium ion transport in the treated myocytes to improve cardiac muscle contractility by diminishing PLB inhibition of SERCA2 activity.

The specification teaches that a MLP knock out (MLPKO) mouse develop dilated cardiomyopathy are mated with a PLBKO mouse and the resulting mice do not develop dilated cardiomyopathy (p 12-13). The specification also teaches point mutations in PLB affect contractility in myocytes in culture (V49A, R14ER, K3ER14E) (p 17). However, the specification fails to correlate the production of said molecules in vitro, to the production of said molecules in vivo, by delivering an expression construct to cardiomyocytes in vivo, wherein the expression of the mutant PLB molecule results in the acceleration of SERCA2 mediated calcium ion transport for improving cardiac muscle contractility associated with heart failure. The specification has failed to correlate the generated knock out mice data with in vitro data. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed method for treating a loss of cardiac muscle contractility associated with heart failure. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

The claims are directed to treatment of cardiac muscle contractility by administring S16E or K3ER14E PLB. The specification has disclosed gene transfer by injecting recombinant adenovirus expressing wild-type and mutant human PLB (sense mutation Val49A), into cardiac myocytes, in vivo, into 1 day old neonatal mouse heart and the isolated cardiac myocytes 4 weeks after injection were identified harboring the mutant transgenes (specification p 28, lines 5-15). However, the specification has not provided any specific guidance that correlates the expression of the mutant Val49A PLB into the cardiomyocytes of the neonatal mouse to delivering an expression construct having S16E or K3ER14E mutation, wherein expression of the polynucleotide accelerates mediated calcium ion transport in the treated cardiomyocytes

resulting in an improvement of cardiac muscle contractility by diminishing PLB inhibition of SERCA2 activity for treating a loss of cardiac muscle contractility associated with heart failure. The specification fails to correlate the direct administration of the Val49S PLB into the cardiac muscle in vivo to the administration of V16E or K3ER14E PLB in cardiac myocytes as in the claimed method.

The art teaches that mutant PLB gene therapy is an unpredictable art with respect to myocardial cell targeting, levels of expression of a therapeutic protein necessary to provide treatment, and mode of administration of the therapeutic gene.

Crystal (Gene Therapy, 10, 2-3, 2003) notes that if you are going to put a gene into a human heart that will be persistently expressed the amount you put in and the place you put it must be absolutely correct (p 3, 2nd column). Once the gene is inserted you cannot simply stop administering the therapeutic protein it produces as is done with conventional drugs (p 3, 2nd column). Crystal notes that ways to regulate the gene expression of the gene of interest or to destroy the cells in which the gene has been placed must be developed (p 3, 2nd column). Moreover, Crystal notes since a strategy of destroying heart cells is not a good idea we will need to adapt promoter control strategies to regulate the expression of the transferred gene (p 3, 2nd column).

Hajjar et al, (PNAS, 95: 5251-5256, 1998) while used a catheter-based technique to achieve cardiac gene transfer in vivo and to alter cardiac function by overexpressing PLB which regulates the activity of SERC2a reports that even though the delivery method was specifically targeted to the heart, they have shown expression of the reporter transgene in other tissues in the body, such as lung and liver but not aorta (p 5255, 2nd column, 2nd paragraph). Crystal reports that other investigators have found extracardiac transgene expression following in vivo injection of adenovirus into the heart when using a nonspecific promoter (p 5255, 2nd column,

2nd paragraph). The use of tissue-specific promoters may obviate this problem in the future (p 5255, 2nd column, 2nd paragraph).

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the delivery of said PLB mutant to cardiac myocytes in vivo to improve cardiac muscle contractility, the lack of direction or guidance provided by the specification fo the delivery of said PLB mutant to cardiac myocytes in vivo to improve cardiac muscle contractility, the absence of working examples that correlate to the delivery of said PLB mutant to cardiac myocytes in vivo to improve cardiac muscle contractility, the unpredictable state of the art with respect to said mutant PLB gene therapy in heart failure and in particular said PLB gene transfer *in vivo* to cardiomyocytes, the undeveloped state of the art pertaining to the delivery of said PLB mutant to cardiac myocytes in vivo to improve cardiac muscle contractility, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Response to Arguments

Applicants argue that the invention claimed is not asserted to be a cure for heart disease. Rather, it is a treatment that beneficially affects SERCA2 function whose physiological relationship to improving cardiac function in heart failure is well known (see, e.g., the inventors' prior issued patent to SERCA2 mediated gene therapy; US Pat. No. 6,605,274; concerning the interaction between PLB and SERCA2, see the discussion in the present Specification at page 2, line 16 through page 5, line 6). Applicants argue to that end, the specification states that the invention provides "methods for treatment of heart failure by inhibiting the effect of PLB on [SERCA2 mediated] Ca2+ uptake in cardiac tissues." (Specification page 6, lines 10-12).

These arguments are not persuasive because no requirement for cure has been implicated in the present office action or in any of the previous office actions. Rather it is stated that there is lack of unpredictability for the treatment of loss of cardiac muscle contractility associated with heart failure. Applicants have not provided guidance for an interaction of PLB and SERCA2 in vivo by administering a construct encoding either a single or double mutant PLB and expressing the molecules in cardiomyocytes in vivo resulting in accelerating SERCA2 calcium ion transport and the improvement of cardiac muscle contractility by diminishing PLB inhibition of SERCA2 activity for treating loss of cardiac muscle contractility associated with heart failure. Thus, applicants have not provided evidence to overcome the unpredictability of PLB gene therapy for reasons set forth in the present and previous office actions.

Applicants argue the art agrees that the invention, as described, does provide the asserted improvement in SERCA2-mediated function in the heart:

> The achievement of Chien and his colleagues is significant in two ways. First, while heart failure can wax and wane, it is a chronic condition requiring persistent therapy. The new study is the first to demonstrate that gene therapy can achieve this. Second, this study shows that enhancement of SERCA function can be used to treat heart failure caused by other defects." (Crystal, Gene Therapy, 10:2-3 (2003), at 3; emphasis added). The foregoing comment was made with respect to the inventors' post-filing published description of the invention as now disclosed and claimed.

Applicants argue whatever concerns the art may or may not have about whether PLB gene therapy will work for cardiac conditions generally, those of skill in the art clearly consider the question to have been resolved for the particular approach taken by the invention to treat heart failure.

In response to applicants discussion of the article by Crystal regarding the significance of enhancement of SERCA function, it is noted that Crystal provides an opinion that enhancement of SERCA function can be used to treat heart failure caused by other defects and do not provide guidance as to how an artisan would have practice a method for treating a loss of cardiac muscle contractility associated with heart failure by delivering a construct with a mutant PLB into cardiomyocytes in vivo, wherein expression of mutant PLB accelerates SERCA2

mediated calcium transport in the cardiomyocytes by diminishing PLB inhibition of SERCA2. These arguments are not persuasive because applicants have not provided evidence to overcome the issues of expression of the said PLB mutants in vivo to achieve enhancement of SERCA function to treat heart failure caused by loss of cardiac muscle contractility. There is no enabled use for no effect.

Applicants argue the Action concerns whether the invention as described is ready for clinical use. In this respect, the Action cites Crystal, supra, as acknowledging that the art was not ready to commence human heart failure gene therapy trials as of early 2003 (Crystal at p. 3; Office Action at p. 8). Zhao, et al. is also cited as being "cautiously optimistic" about the clinical prospects for the invention, subject to further research. (Zhao, et al. at p. 214; Office Action at p. 9). Applicants respectfully submit that the clinical status of the invention for use in humans is not pertinent to the question of whether the claimed invention is enabled. Clinical efficacy and safety are not issues within the view of the Patent Office, but are instead exclusively matters of concern to the Food and Drug Administration. Moreover, the fact that further experimentation may be required to advance the invention into human use, even if true, does not establish that the invention is not enabled.

These arguments are not persuasive because no such requirement for clinical efficacy has been implicated in the present or in any of the previously mailed office actions. The MPEP states the examiner cannot ask for clinical trial data regarding safety or efficacy for enablement. No such requirement is in the present record. Applicants claims encompass delivering a construct with mutant PLB in cardiomyocytes in vivo, wherein expression of the molecule accelerates SERCA2 mediated calcium transport in the treated cardiomyocytes for treating loss of cardiac muscle contractility. Applicants have not shown such an effect with any construct containing a PLB mutant. There is no enabled use for no effect. The MPEP has not prohibition

as to reviewing clinical trial data to determine enablement at the time of filing. No body of evidence is removed from consideration by the MPEP. As for treating loss of cardiac muscle contractility associated with heart failure by way of the claimed methods, evidence presented in the art provide evidence for unpredictability. In the present situation, the cited references by the applicants all together establish at the time of filing the claimed methods lacked enablement as the skilled artisan would have needed to perform an undue amount of experimentation without a predictable degree of success to implement in the invention as claimed.

Applicants argue with respect to gene therapy directed at SERCA2 function in the heart, only two potential avenues for further experimentation are noted in the art of record as predicates for human clinical use of such therapy: the identification of optimal promoters for expression vectors (Crystal, supra at 3) and, for initial studies, the use of sufficiently informative animal models (Zhao, supra at 214-215, bridging paragraph). In the first respect, while efforts to improve available expression constructs are ongoing in the gene therapy art, viral constructs of the kind utilized by the inventors have been used in the heart from a time preceding the filing date of the present application1, and have been approved by the FDA for human clinical trial use in SERCA2 gene therapy (see, e.g., clinical trial NCT00454818, Phase I, ww.clinicaltrials.). Therefore, while further improvements to gene therapy expression vectors are desirable, the constructs existing at the time the present application was filed were sufficient to enable the art to practice the invention without undue experimentation. See, e.g., U.S. Patent No. 6,605,274, filed April 1995, claiming a method for SERCA2 gene therapy using adenoviral vectors; U.S. Patent No. 5,797,870, filed March 1995, claiming a method for introducing a "gene therapy agent" into the pericardium using expression vectors such as adenoviral vectors and adeno-associated virus vectors; U.S. Patent No. 5,919,449, filed May, 1995 claiming an ex vivo

method for implantation of porcine cardiomyocytes transfected with a viral expression vector into the heart, to treat conditions such as congestive heart failure; U.S. Patent 6,162,796, filed September, 1995, describing use of AAV vectors in particular to deliver therapeutic genes to the heart to treat cardiac disorders; and, U.S. Patent No. 6,306,830, filed September, 1996, identifying vectors desirable for use in treating congestive heart failure as including then known adenoviruses, adeno-associated viruses, and retroviruses.

These arguments are not persuasive because although specific vectors, promoters, genes, and routes of administration might be or may have been effective for treatment of a specific disease providing a specific therapeutic effect, gene therapy as a broad-based art is clearly unpredictable in terms of achieving levels and duration of expression of a gene of interest in a therapeutic effect. In the instant case, it is unpredictable the expression of a therapeutic amount of a mutant PLB sufficient to accelerate SERCA2 mediated calcium ion transport in vivo resulting in the improvement of cardiac muscle contractility by diminishing PLB inhibition of SERCA2 activity.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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